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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,803	02/05/2001	Vanitha Ramakrishnan	044481-5044	3916

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,803	RAMAKRISHNAN ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 October 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Final Rejection

Claims 1-27 are pending examination.

Applicants' traversal, the amendment to claims 1, 3, 5, 10, 15, 21, 23, and 25 in paper no. 12 is acknowledged and considered.

The objections to claims 1, 5, 10, 15, 23 are moot in view of the amendment to the claims.

Oath/Declaration

The oath filed on 9/10/02 has been entered with the signature of the second inventor. Absence evidence to the contrary, the notice of submitting another petition (See paper no. 12, page 4) is moot in view of the oath filed on 9/10/02.

Drawings

BL 12/18/02

NOTE: In the next response, please submit a response to the PTO 948 because a PTO 948 was filed with the ~~non-~~final rejection dated 1/30/01 and the applicants have not submitted proposed corrections to the drawings. If the reply to the Final Rejection does not have a response to the 948, the response will be considered non-responsive. See 37 CFR 1.85(a).

The rejection to claims under 101 is moot in view of the applicants' traversal. See pages 5-8.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-27, as best understood, are readable on a genus of a non-human transgenic animal comprising either a modified, a non-functional, or a disrupted glycoprotein (GP) V gene, wherein the genus of the transgenic animal is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 15-20, as best understood, are readable on a genus of a biological response of a non-human transgenic mammal modified GP V gene, wherein the genus of the biological response is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 21-22, as best understood, are readable on a genus of a characteristic of an animal that is attributable to the expression of the GP V gene, wherein the genus of the characteristic is

not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates a genus of transgenic animals, which the GPV gene has been modified so that the animals do not express a functional GPV protein or expresses a GPV protein that demonstrates a reduced functionality as compared with the native or wild type GPV protein (page 1). The specification provides description of a species of a modified mouse GPV gene, which when the non-functional gene is transfected into a cell results in no expression of the GPV protein (pages 14-15).

In addition, the specification contemplates a characteristic between two animals of the same species, wherein one animal has for example a wild type GPV gene and the other animal has a modified GPV gene (page 3). The specification provides sufficient guidance of a species of characteristics from a transgenic mouse with a non-functional GPV gene, which are: an increased sensitivity to platelets from the transgenic mouse to activation by low concentrations of thrombin and a decrease bleeding time of the transgenic mouse compared to a wild type mouse. Furthermore, the specification provides sufficient guidance of a species of a biological response from a transgenic mouse with a non-functional GP V gene, which is an increased sensitivity to platelets from the transgenic mouse to activation by low concentrations of thrombin.

However, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of a biological response of a non-human transgenic mammal modified GP V gene and/or the genus of a non-human transgenic animal comprising a modified or a non-functional GP V gene and/or the genus of a characteristic of an animal that is attributable to the expression of the GP V gene as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of a non-human transgenic animal comprising a modified GP V gene or a non-functional GP V gene and/or the genus of a characteristic of an animal that is attributable to the expression of the GP V gene and/or the genus of a biological response of a non-human transgenic mammal modified GP V gene. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of a non-human transgenic animal comprising a modified GP V gene or non-functional GP V and/or a genus of a characteristic of an animal that is attributable to the expression of the GP V gene and/or a genus of a biological response of a non-human transgenic mammal modified GP V gene that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement.

Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a non-human transgenic animal comprising a modified GP V and/or a genus of a characteristic of an animal that is attributable to the expression of the GP V gene and/or a genus of a characteristic of an animal that is attributable to the expression of the GP V gene that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicants traverse the 112 written description rejection for the following reasons: The specification demonstrates possession by actual reduction to practice and by a description with sufficient relevant identifying characteristics to allow one skilled in the art to recognize applicants were in possession of the claimed invention. The specification discloses the nucleotide sequences for the human, mouse and rat. The specification further provides results showing the effect of knocking out GPV gene expression in a transgenic mouse. In light of the highly conserved nature of the gene, one of ordinary skill in the art would find adequate

guidance and written description to practice the invention across the full scope of the inventions as claimed. See pages 9-10.

Applicants' traversal is acknowledged and is found partially persuasive. The specification provides description of a species of a modified mouse GPV gene, which when the non-functional gene is transfected into a cell results in no expression of the GPV protein. However, the specification does not provide sufficient description of species of GPV genes to represent the genus of GPV genes including sheep, goat, pig, cat, monkey, rabbit, cow, snake, shark, nematode, or guinea pig. The traversal states, "the mouse and rat coding sequence are more homologous than human and mouse GPV sequences" (page 9). It is apparent from the state of the prior art exemplified by Ngo *et al.* (The Protein Folding Problem and Tertiary Structure Prediction, Birkhauser Boston, 1994, pp. 491-494) and Chiu *et al., Folding and Design*, 1998, pp. 223-228) that the description of the primary sequence of amino acid residues in which the positions of the amino acid residues are particularly arranged is essential for the biological function of the protein encoded by the sequence. This essential element that is required for an adequate description of a representative number of species as embraced by the claimed genus of GPV encoded nucleic acid sequences is neither described sufficiently in the specification nor conventional in the prior art. A mere statement asserting that by providing the human, rat and mouse GPV sequence is a representative number of sequences without providing the essential and specific arrangement of the amino acid residues positioned in the sequence does not lend evidentiary support for a skilled artisan to have recognized that applicant was in possession of the genus of GPV encoded nucleic acid sequences as claimed, particularly since the essential element of the coding sequence of a generic GPV is lacking from the as-filed

specification and since the skill and knowledge in the art is not adequate or conventional to determine the primary sequence of the representative number of species of GPV encoded genes or nucleic acids on the basis of the only disclosure of human, rat, and mouse sequences.

Vas-Cath Inc. v Mhurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purpose of the 'written description' inquiry, *whatever is now claimed*." The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath, See MPEP 2163).

The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or the simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v Chugai Pharmaceutical Co. Ltd., 18 USPQ 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification only provided the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997): *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement 'by describing the invention, with al it claimed limitations, not that which make it obvious," and by using

> "such descriptive means as words, structures, figures, diagrams, formulas, etc. that set forth the claimed invention." *Lockwood*, 107F.3d at 1572, 41 USPQ2d at 1966.

> An adequate written description of a DNA, such as the cDNA of the recombinant plasmid and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Dir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. At 1170, 25 USPQ at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information, concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is not further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes; as the example does, does not necessarily describe the cDNA itself. No sequence information indication which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, the claimed invention provides sufficient description of the rat, mouse and human GPV nucleotide sequences, but not for the full breadth of the claims (or none of the sequences encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Furthermore, with respect claims 15-22, encompassing a characteristic or a biological response of a non-human animal that is attributable to the expression of the modified glycoprotein V gene. The specification provides sufficient description of a species of characteristics or biological responses from a transgenic mouse with a non-functional GPV gene, which are: an increased sensitivity to platelets from the transgenic mouse to activation by low

concentrations of thrombin and a decrease bleeding time of the transgenic mouse compared to a wild type mouse. The specification does not provide sufficient description of a representative number of characteristics or biological responses (e.g. inflammatory response, angiogenic response, etc.) of a non-human animal that is attributable to the expression of the modified glycoprotein V gene other than the response set forth above.

Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A transgenic mouse comprising a homozygous disruption of a gene encoding GP V protein in its somatic and germ cells, wherein said disruption results in an increased sensitivity to platelets, activation by low concentrations of thrombin, and a decrease bleeding time compared to a non-transgenic mouse; 2) A method of producing the transgenic mouse of 1) using embryonic stem cells, wherein the somatic and germ cells of said mouse contain a disrupted GP V gene, which comprises: a) introducing into mouse embryonic stem cells a nucleic acid construct that disrupts the GP V gene; b) injecting the embryonic stem cells containing the disrupted GP V gene into mouse blastocysts; c) implanting the blastocyst into a pseudopregnant mouse; d) allowing the embryo to develop producing a mouse comprising a disrupted GP V gene in its germ line; e) breeding said mouse to generate a heterozygous mouse comprising a disrupted GP V gene; and g) interbreeding said heterozygous mice and selecting progeny that are homozygous for said disrupted GP V gene; 3) A method of identifying an agent that modulates a thrombotic response of a transgenic mouse comprising a homozygous disruption of a gene encoding GP V protein in its somatic and germ cells, comprising: a) administering an agent to the mouse, b) cutting the tail of the mouse from step a); and c) determining whether the bleeding time is increased or decreased compared to a non-transgenic

mouse, and does not reasonably provide enablement for the full scope of the claimed embodiment (using ES cells to produce a non-human animal comprising a modified GPV gene). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification discusses that the invention features a genus of transgenic non-human mammals comprising either a non-functional GPV gene or a modified GPV gene and goes on to contemplate that there are two techniques for producing the transgenic animals (pages 5-13). The specification provides prior art pertaining to methods for generating transgenic mammals using fertilized eggs and pro-nuclei injection. In addition, the as-filed specification provides the second method for producing transgenic mice, which involves modification of embryonic stem cells using transgenic DNA.

The specification requires that the starting material, which is a nucleic acid encoding a GPV polypeptide, be used in a method of making a transgenic non-human mammal comprising either a modified or a non-functional GPV gene. The specification provides prior art pertaining to the preparation of transgenic mice that were well known in the art (page 12). For example, a transgene can be introduced into the germline of a transgenic mouse by microinjection for production of a transgenic mouse. The specification displays one method of generating the

transgenic non-human mouse: 1) The DNA sequence encoding GPV comprising a coding region of mouse GPV (including the putative initiator Met to Leu^{389}) was replaced by a neo cassette and injected the vector into an ES cell line (pages 14-15). The neo clones were identified by positive selection and the clones were injected into embryos from C57BL/6J mice (page 15). Furthermore, the disclosure provides characterization of the effect of GPV gene deletion on thrombin-induced platelet function at low concentrations of thrombin (Example 5, pages 22-23). Furthermore, in example 6, the specification displays the GP V-/- mice have a decrease bleeding time in vivo compared to +/+ mice and +/- GPV mice (page 23-24). The specification contemplates that the transgenic mice can be used in a method for identifying agents that modulate a biological response (e.g. thrombotic or pro-thrombotic) (pages 25).

It is further to note that the as-filed specification only contemplates the use of embryonic stem (ES) cell technology or using pro-nuclear injection for the generation of transgenic mammals for used in the claimed invention. See pages 5-13 of the specification. The state of the art at the time application was filed for producing transgenic animals using pro-nuclear injection was considered unpredictable as exemplified by Polejaeva et al. Theriogenology, Vol. 53, pages 117-126, 2000, Polejaeva states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. See page 119.

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system, at present and that only "putative" ES cells exist for other species. See Rulicke et al. (Experimental Physiology, Vol. 85, 2000, page 2092), who supports this observation. Rulicke et al. disclose, "The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far." Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Reprod. Nutr. Dev, 1998, Vol. 36, pages 607-618) teaches that:

> The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species. See page 608.

As the claims encompass a transgenic animal comprising modified ES cells by using any technology, and the as-filed specification fails to teach the establishment of true ES cells for use in the production of any transgenic animal other than mice, the state of the art supports that only mouse ES cells were enabled for used in the production of transgenic mice. In view of the concerns set forth by the state of the art, the examples do not reasonably address the concerns put forth by the state of the art encompassing any method for producing transgenic animals for use in addressing the role of GPV or identifying agents that modulate a biological response in the transgenic animal. In view of these factors and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate from the specification and the prior art to any method of producing transgenic animals comprising a non-functional GPV gene other than a mouse. However, in view of the concerns stated above encompassing microinjection and

random integration into a mammal's genome it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from random integration to determining if a DNA sequence encoding the GPV polypeptide is inserted at the correct site and is expressed at a level sufficient enough to produce a phenotype in any transgenic non-human animal other than a mouse.

In addition, the disclosure fails to provide any relevant teachings or sufficient guidance with regards to the production of any transgenic animal comprising a transgenic sequence encoding a modified GPV, which expresses the transgenic sequence such that a phenotype occurs other than a mouse with a homozygous disruption of a gene encoding GP V. Furthermore, the as-filed specification fails to describe any particular phenotype exhibited by any transgenic animal of the invention other than the mouse comprising a homozygous disruption of a gene encoding GP V protein in it somatic and germ cells. The specification displays that mice with a heterozygous non-functional GP V gene have the same bleeding time as wild type mice. Thus, as enablement requires the specification to teach how to make and/or use the claimed invention, the specification fails to enable the production of any transgenic animal comprising a modified GPV gene other than a mouse with a homozygous disruption of a gene encoding GP V.

[Note that although the claimed transgenic animal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their

broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic animal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic animal would serve if the transgene (e.g. GP V) is not expressed at a sufficient level for a resulting phenotype).]

As the specification fails to provide any relevant teachings or sufficient guidance with regard to the production of a representative number of transgenic non-human animals as claimed other than a mouse with a homozygous disruption of a gene encoding GP V, one skilled in the art would not be able to rely on the state of the art for an attempt to produce any transgenic animal other than mice with a homozygous disruption of a gene encoding GP V. This is because of the art of transgenic is not predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic animal comprising a transgene of interest (e.g. GPV); it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For example, the level and specificity of expression of a transgene (e.g. GPV) as well as the resulting phenotype of the transgenic animal are directly dependent on the specific transgene construct. The individual gene of interest, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of genetically modified animals, which exhibit a particular phenotype. This observation is supported by Wall (Theriogenology, 1996) who states "Our understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61,

last paragraph. See also Houdebine (Journal of Biotechnology, 1997) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g. specific promoters, presence or absence of introns, etc. The specification does not provide sufficient guidance, and it fails to feature any reasonable correlation between producing transgenic animal using microinjection of transgene into germ line and producing a transgenic animal, which comprises a transgenic sequence encoding either a modified GPV and which the protein in the transgenic mammal, and, thus, a specific resulting phenotype other than a transgenic mouse with a homozygous disruption of a gene encoding GP V.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins states that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report "transgene expression and the physiological consequences of transgene in animals are not always predicted in transgenic mouse studies." See page 62, first paragraph. Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (page 239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of a representative number of transgenic animal comprising a

modified GPV gene, it would require an undue amount of experimentation to reasonably predict the results achieved in any transgenic animal comprising a transgenic sequence encoding a GPV polypeptide and which expresses the protein in the transgenic animal at the levels of the claimed product, the consequences of that production, and therefore, the resulting phenotype.

As stated above, the specification provides a transgenic mouse comprising a homozygous disruption of a gene encoding GPV polypeptide in its somatic and germ cells wherein said disruption results in increased sensitivity to of platelets to activation by low concentrations of thrombin and a decrease bleeding time compared to a non-transgenic mouse and a method of making the transgenic mice. However, in addition to the art of record encompassing the unpredictability of producing transgenic mice and the breadth of the claims, the art of record for GP V teaches that the role of GP V is poorly defined (IDS, Dong, pages 4355 and 4362). This is further supported by Kahn (Blood, Vol. 94, 1999, pp. 4112-4121), Kahn produces GPV-deficient mice using gene targeting, wherein the entire GPV gene was knock out and shows that the mice responded normally to thrombin and that the tail-bleeding times of wild type and GPV deficient mice were indistinguishable (pages 4114-4115). In view of Kahn, this research further supports that the full breadth of the claimed invention is not enabled and it would take an undue amount of experimentation to reasonably extrapolate from a transgenic mouse comprising a homozygous disruption of a gene encoding GPV polypeptide to any other transgenic animal comprising a non-functional GPV gene.

If the applicants are able to overcome the 112 rejection for producing any transgenic animal using ES cells and correlating the phenotype observed in a transgenic mouse with a

homozygous non-functional disruption of the GP V gene to the phenotype produced in any other transgenic non-human animal, there is a rejection under enablement for claims 15-22.

Furthermore, with respect to claims 15-22, which read on an *in vivo* method for identifying an agent that modulates a biological response of a non human animal comprising a non-functional GPV gene, the specification and the state of the art do not provide sufficient guidance for one skilled in the art to monitor any biological response of an agent in an vivo or in vitro assay in said transgenic animals other than the bleeding time of a transgenic mouse comprising a homozygous disruption of a gene encoding GPV polypeptide. The specification and art of record do not provide sufficient guidance for one skilled in the art to reasonably correlate from a bleeding time assay to any other in vitro assays or in vivo assays without an undue amount of experimentation. In addition, the specification displays that the bleeding time of a mouse with heterozygous non-functional GP V gene is similar to a wild-type mouse. With respect to claims 21-22, which encompass a method of determining the effect of an agent on a characteristic of a transgenic mouse that is attributable to the expression of the GPV gene, the specification does not provide sufficient guidance for any characteristic of a transgenic animal other than the following characteristics for a transgenic mouse with a homozygous non-functional disruption in the GP V gene: increased sensitivity to platelets, activation by low concentrations of thrombin, and a decrease bleeding time compared to a non-transgenic mouse. Thus, in view of the breadth of the claims and the lack of sufficient guidance provided by the specification, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the characteristics listed above to any other characteristics encompassed by the claimed method. Therefore, it would take an undue amount of

experimentation to reasonably correlate to any other characteristic not provided by the specification that is attributable to the modified expression (mis-expression or no expression) of the GPV gene.

In conclusion, in view of the quantity of experimentation necessary to determine the parameters listed above for the starting material, a transgenic non-human animal comprising a non-functional or modified GP V gene, the lack of direction or sufficient guidance provided by the as-filed specification for the production of a transgenic non-human animal other than a transgenic mice with a homozygous non-functional disruption in the GP V gene, the claimed invention is only enabled for 1-3 listed above. Furthermore, the working examples for the demonstration or the reasonable correlation from a transgenic mouse with a homozygous disruption of the GP V gene to the production of any other transgenic animal, in particular when the expression of the GP V gene must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to the transgene behavior in transgenic non-human mammals of any species, and the breadth of the claims drawn to any transgenic non-human mammal, it would require an undue amount of experimentation for one skilled in the art to make and/or use the full breadth of the claimed invention.

Applicants traverse the rejection of claims 1-27 under 112 enablement for the following reasons: The citation of Polejaeva et al about a "serious limitation" in a technique about producing transgenic animals does not rise to the level of undue experimentation. That is only one factor. The limitations discussed in the office action are routine problems encountered in experimental protocols and undue amount of experimentation is not required for the production of transgenic animals having the desired phenotype. The office has not established adequate

reasons why undue experimentation would be required in view of the disclosed methods and obtained results. Detail protocols are readily available for producing transgenic animals are readily available to one skilled in the art. The specification discloses that transgenic procedures have been successfully used in a variety of non-murine animals. A phenotype for the transgenic mice is disclosed on page 21. To the extent that the Kahn's results differ from the results presented herein, those differences may be attributable to different methodologies and reagents used. See pages 10-14.

Applicants' traversal is acknowledged and is found partially persuasive for 1-3) listed above, however the full scope of the claimed invention is not considered enabled. The claims recite only using embryonic stem cells (and not hematopoietic stem cells) for producing non-human transgenic animals comprising a modified GP V gene. The art of record at the time the application was filed discloses, "The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far (Rulicke)." Furthermore, for chromosomal insertion of DNA into a genetically modified animal as exemplified by the claims the art of record further teaches that: The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species (Bishop, Reprod. Nutr. Dev., 1998, Vol. 36, pages 607-618). In view of the art of record ES technology has been successful only in mice, the as-filed specification only provides sufficient guidance for one skilled in the art to make and use murine ES cells for

producing the claimed transgenic mice. It is acknowledged that pro-nuclear injection has been used to produce other types of transgenic non-human animals, but pro-nuclear injection is not recited in the claims and is different from ES technology and does not reasonably correlate to using ES technology to produce any type of transgenic non-human animal. Furthermore, U.S. Patent 5,589,369 cited in the applicants' traversal was only enabled for *in vitro* use of mammalian cells (see claims of patent '369); US Patent 5489,743 also cited uses pro-nuclear injection and was only enabled for the production of transgenic mouse (see claims of patent '743); U.S. Patent No. 5,602,307 also cited was only enabled for using murine ES cells for the production of transgenic mouse (see claims of patent '307). The specification fails to provide sufficient guidance or evidence to overcome the problems with ES technology provided by the art of record. Thus, the specification fails to provide sufficient guidance for one skilled in the art to reasonably extrapolate form making and using murine ES cells to using any other type of ES cells.

In addition, the art of record displays that transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination. The specification provides sufficient guidance for a phenotype of a transgenic mouse that has a homozygous non-functional disruption of the GP V gene, but does not provide sufficient guidance for a transgenic animal (mouse) with reduced functionality as compared with a native or wild type GP V protein. The specification and applicants' traversal only provide sufficient guidance for how to use the transgenic GP V mouse (-/-) described above in a diagnostic method contemplated by the claims and does not provide sufficient or evidence for how to use transgenic GP V mouse with a (+/-) because its

bleeding time and response to thrombin are similar to a wild-type mouse. The art of record displays the unpredictability of correlating a phenotype from one species to another species and the specification and applicants' traversal fail to provide sufficient guidance for how to overcome the unpredictability set forth by the art of record (See Wall, Strojek and Wagner, and Mullins). The specification only provides one species (mouse with a homozygous non-functional disruption of GP V gene). Thus, in view of the In Re Wands Factors, the claimed invention is only enabled for 1-3 listed above and not for the full breadth of the claimed invention.

Furthermore, applicants traverse the rejection for claims 15-22 for the following reasons: The specification discloses several assays used to detect GPV expression and those assays can be used irrespective of animal type, See examples 4-6. Applicants strongly disagree with the statement that no characteristic is enabled by the specification. The specification discloses results, showing characteristics of the GPV -/- transgenic mice on pages 21-24. The specification provides the requisite amount of necessary guidance for a method of identifying an agent that modulates a biological response of a non-human transgenic animal. See pages 14-16.

With respect to the traversal for claims 15-22, the as-filed specification and the state of the art do not provide sufficient guidance for one skilled in the art to monitor any biological response of an agent in an vivo or in vitro assay in said transgenic animals other than the bleeding time of a transgenic mouse comprising a homozygous disruption of a gene encoding GPV polypeptide. The specification and art of record do not provide sufficient guidance for one skilled in the art to reasonably correlate from a bleeding time assay to any other in vitro assays or in vivo assays without an undue amount of experimentation. In addition, the specification

displays that the bleeding time of a mouse with heterozygous non-functional GP V gene is similar to a wild-type mouse. Furthermore, with respect to claims 21-22, which encompass a method of determining the effect of an agent on a characteristic of a transgenic mouse that is attributable to the expression of the GPV gene, the specification does not provide sufficient guidance for any characteristic of a transgenic animal other than the following characteristics for a transgenic mouse with a homozygous non-functional disruption in the GP V gene: increased sensitivity to platelets, activation by low concentrations of thrombin, and a decrease bleeding time compared to a non-transgenic mouse. Thus, in view of the breadth of the claims and the lack of sufficient guidance provided by the specification, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the characteristics listed above to any other characteristics encompassed by the claimed method. Therefore, it would take an undue amount of experimentation to reasonably correlate to any other characteristic not provided by the specification that is attributable to the modified expression (mis-expression or no expression) of the GPV gene.

The rejection of Claims 3, 5, and 15-22 under 112 second paragraph are moot in view of the amendment to the claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

Brian Whiteman
Patent Examiner, Group 1635
12/26/02